REMARKS

Claims 11-22 are in the application. No claim is allowed.

Claims 11, 13 and 14 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Finkenaur et al., of record ("Finkenaur"). The examiner refers to a composition on page 8, example 4 of Finkenaur that contains hyaluronic acid, EGF (epidermal growth factor) and water. Claims 11, 13 and 14 of the present application recite a composition comprising an effective amount of growth factor, hyaluronic acid and excipients to maintain biological activity of the factor wherein the composition is sufficient to enhance bone growth rate and magnitude, having a viscosity and biodegradability sufficient to persist at a site of desired bone growth for a period of time sufficient to enhance to the bone growth rate and magnitude. The examiner considers water to be an excipient in Finkenaur's composition. However, the current claims call not for merely an excipient, but an excipient that maintains the biological activity of the growth factor at the site of application. Such excipients comprise buffer salts, sugars, anti-oxidants or preservatives. See page 3, lines 4-7, of the specification. In Examples 1-5 in the present application, the hyaluronic acid-growth factor compositions of the invention used in the experiments all contain sugar, sodium citrate and EDTA.

Accordingly, it is submitted that Finkenaur does not anticipate the present claims since it lacks a teaching of the required excipients recited in the present claims. Withdrawal of this rejection is therefore respectfully requested. Also, in this rejection the examiner cites a reference Mori et al. Applicant cannot find a citation of this reference in the record. It is requested that the examiner provide the citation details of this reference so that Applicant may study it and comment.

Claims 11-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Finkenaur. This rejection is respectfully traversed. The examiner considers water to be an excipient in the composition and therefore apparently does not consider Finkenaur as lacking in a teaching of this element. However, as discussed above, the present claims recite an excipient to maintain the

biological activity of the growth factor. Finkenaur does not teach that water alone is such an excipient. Therefore, the composition in the example 4 of Finkenaur, relied upon by the examiner, fails to meet this requirement. There is no motivation in Finkenaur to modify the composition of example 4 with buffer salts and sugars, and the like. While Finkenaur does state on page 5, lines 42-45, that cellulose derivatives are capable of stabilizing polypeptide growth factors against loss of biological activity, it is not taught that hyaluronic acid alone serves this purpose. Therefore, if anything, Finkenaur directs, as shown on page 4, lines 55-58, that if one wants to maintain the biological activity of the EGF one should use a cellulose derivative as the polymeric component of Finkenaur's composition, instead of hyaluronic acid. This is a teaching away from the present invention.

In the final rejection, in the "Response to Arguments" on page 7, the examiner apparently makes an argument on inherency, stating that Finkenaur's composition must be sufficient to enhance bone growth rate and magnitude and has a viscosity and biodegradability sufficient to persist upon application at a site of desired bone growth for a period of time "since it enhances said bone growth rate and magnitude." This is the same rejection, stated differently, as that made under 35 USC 102 discussed above. It is not seen where Finkenaur teaches that a composition of growth factor, hyaluronic acid and excipients to maintain biological activity of the factor enhance bone growth rate and magnitude. Finkenaur's composition lacks the requisite recipient. Furthermore, in Table 4 shown on Applicant's specification at page 10, it is shown to be unpredictable as to the combinations of growth factor and carriers that will be advantageous for bone formation. A mixture of bFGF in 2% HA (and sucrose, sodium citrate and EDTA) achieves high bone formation scores of 3 and 4. However compositions of bFGF in 2% collagen or 2% dextran sulfate resulted in low bone formation scores. Therefore, it is not seen how Finkenaur either shows that a composition of growth

factor and HA enhanced bone growth rate and magnitude as required by the present claims or how Finkenaur suggests to one of ordinary skill in the art that such a composition enhances bone growth rate and magnitude as required by the claims. For the foregoing reasons it is submitted that the claims are unobvious over Finkenaur and withdrawal of this rejection is respectfully requested.

Claims 17-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dunstan et al., ("Dunstan") of record, in view of Brismar, of record. This rejection is respectfully traversed. The examiner cites page 15, lines 2-25 in Dunstan. In that passage, there is disclosed Table 2 showing the effects of bone growth of two carriers, PBS and PBS plus heparin, and two formulations of aFGF and bFGF, either alone or with heparin. Studying the results on that table, it is submitted that one of ordinary skill in the art would be led to use bFGF alone or bFGF plus heparin. aFGF is inferior and the carriers stimulate no endosteal bone growth. This is further confirmed in the claims in Dunstan in which the only active ingredient claimed is the growth factor in a composition (independent claims) and the growth factor in combination with heparin (claim 11). Dunstan lacks a teaching of the use of hyaluronic acid in the composition and a teaching of the sufficient viscosity and biodegradability sufficient to persist upon application at the site of desired bone growth for a period of time sufficient to enhance the bone growth rate and magnitude. Since Dunstan administered the growth factor as a solution, retention at the site of desired bone growth was not an issue. Obviously the solution dissipated rather quickly from the site of application.. In order to compensate for this, apparently Dunstan administered the solution four times a day. Therefore, Dunstan completely misses the feature of enhancing bone growth rate and magnitude while persisting at the site of desired bone growth. Dunstan also fails to teach the use of hyaluronic acid.

The examiner relies on Brismar to show the use of hyaluronic acid for treatment of bone fractures. However, there is no motivation in Brismar, nor in Dunstan, to modify the compositions

of Dunstan by addition of hyaluronic acid. As discussed above, one of ordinary skill in the art upon reading Dusnstan would see from the data that growth factor alone or the growth factor in combination with heparin, should be used. Applicant's own data, in Table 4 of the specification, suggests that combinations of growth factor with other carriers leads to unpredictable results. Furthermore, Applicants traverse the suggestion by the examiner that Brismar discloses that hyaluronic acid can be used to treat bone fractures. Brismar discloses the use of 0.1 to 2% hyaluronic acid gels to treat varicose ulcers caused by diabetes. All of the tests and examples in Brismar are directed to the treatment of ulcers caused by diabetes and the methods disclosed are directed through topical administration to the ulcer. See col. 2, line 66 and col. 2, lines 22-30. According to Brismar, the gel is suitably effective by application once or twice a day with coverage by a bandage. What would be the function, as directed by the teachings of Brismar, of adding hyaluronic acid to compositions disclosed by Dunstan? There is no motivation to make such modification. There is no suggestion in Brismar that addition of hyaluronic acid to a growth factor-containing composition would improve the effect of the growth factor. Indeed it can be argued that Dunstan teaches away from adding hyaluronic acid or any other additional component, other than heparin.

It is submitted that there is no recognition by either Dunstan or Brismar of the desirability of applying a composition at the bone defect and allowing the composition to persist at the site for a period of time sufficient to enhance the bone growth rate and magnitude where the composition comprises an effective amount of growth factor, hyaluronic acid and excipients to maintain biological activity of the factor. Moreover, the hyaluronic acid gradually dissipates from the site of application by biodegradation. There is no recognition by either Dunstan or Brismar of the biodegradation properties to match the required persistence at the bone defect. Both Brismar and

Dunstan apply their compositions at least daily and sometimes multiple times daily so they are not concerned with persistence at the site of application.

It is thus submitted that the claims are unobvious over this combination of references and withdrawal of the rejection is respectfully requested.

It is submitted that the application is in condition for allowance.

If prosecution of this application can be assisted by telephone, the Examiner is requested to call Applicants' undersigned attorney at (510) 663-1100.

Please apply any other charges or credits to deposit account number 50-388 (Order No. DEPYP003D1C1).

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